

Gene Section

Review

CYLD (cylindromatosis (turban tumor syndrome))

Gilles Courtois

INSERM U781, Hopital Necker-Enfants Malades, Paris, France (GC)

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Identity

Other names: CDMT, CYLD1, CYLDI, EAC, FLJ20180, FLJ31664, FLJ78684, HSPC057, KIAA0849, MFT, MFT1, SBS, TEM, USPL2

HGNC (Hugo): CYLD

Location: 16q12.1

Local order: ...NOD2, CYLD, SALL1 (Rev)...

DNA/RNA

Description

21 exons (17 coding) with alternative splicing (see figure 1). Size of the exons: 74 (bp), 98, 79, 136, 626, 302, 105, 8, 98, 116, 379, 165, 141, 122, 91, 66, 132, 108, 118, 216, 5611. The whole gene extends over approximately 56 kb.

Pseudogene

No.

Protein

Description

956 aa, approximately 110 kD.

Member of the deubiquitinase family (USP (Ubiquitin Specific Protease)) (Reyes-Turcu et al., 2009) with preferential affinity for K63-linked polyubiquitin chains (Massoumi and Paus, 2007; Courtois, 2008).

Expression

Ubiquitous.

Localisation

Cytoplasm (might bind to microtubules through its CAP-Gly domains).

Function

CYLD has been primarily identified as a negative regulator of NF-kappaB signaling, able to bind NEMO and TRAF2 and to deubiquitinate them (Brummelkamp et al., 2003; Kovalenko et al., 2003; Trompouki et al., 2003). It is also a negative regulator of JNK and p38 signaling pathways (Reiley et al., 2004) and IRF-3 signaling pathways (Friedman et al., 2008; Zhang et al., 2008). It participates in antimicrobial defense and inflammation by targeting ubiquitinated TRAF6 (Lim et al., 2007; Lim et al., 2008) and is required for the development and activation of immune cells (Reiley et al., 2006; Jin et al., 2007).

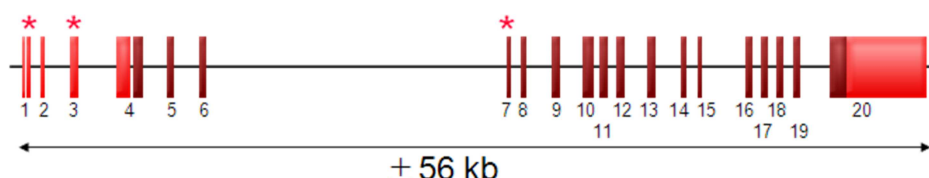


Figure 1. CYLD gene. Coding exons are indicated in dark red. Asterisks indicate exons which are differentially spliced. One of the exon which is alternatively present (Reiley et al., 2004) encodes the binding site for TRAF2 and NEMO (Hövelmeyer et al., 2007).

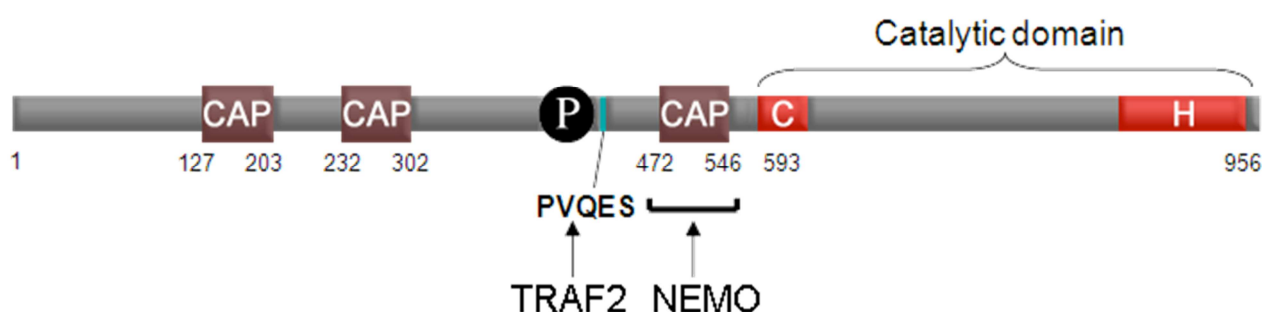


Figure 2. Structural organisation of CYLD. Binding sites for TRAF2 and NEMO are indicated. CAP: CAP-Gly domain, P: phosphorylation site, C and H: subdomains of the catalytic domain containing the Cys and His active residues.

CYLD may also affect cell proliferation/cell cycling by targeting Plk1 and HDAC6 (Stegmeier et al., 2007; Massoumi et al., 2009) and cell migration via microtubule assembly (Gao et al., 2008). It controls spermatogenesis by deubiquitinating RIP (Wright et al., 2007) and osteoclastogenesis by deubiquitinating TAK1 (Jin et al., 2008). A role for CYLD in the hypoxia response has been reported (An et al., 2008). Its inactivation by human papilloma virus-derived E6 protein results in hypoxia-induced NF-kappaB activation. Finally, it has been shown to affect calcium channel function by deubiquitinating TRPA1 (Stokes et al., 2006).

CYLD interacts with NEMO (Kovalenko et al., 2003; Trompouki et al., 2003), TRAF2 (Kovalenko et al., 2003; Trompouki et al., 2003), p62 (Wooten et al., 2008), Bcl-3 (Massoumi et al., 2006), TAK1 (Reiley et al., 2007), RIP (Wright et al., 2007), Ick (Reiley et al., 2006), HDAC6 (Wickström et al., 2010).

Homology

Catalytic box (with other members of the deubiquitinase family (USPs)) and CAP-Gly (with a small collection of proteins (Steinmetz and Akhmanova, 2008)).

Mutations

Germinal

Tumor suppressor (Bignell et al., 2000).

See full recent listing in Blake and Toro, 2009. Most of the mutations (non sense, frameshit, splicing) would produce large deletions of the protein but, most likely, produce mRNA nonsense-mediated decay. Short truncations affect the catalytic box which extends to the carboxy-terminus of the protein and produce an inactive enzyme. Very few missense mutations have

been reported. All of them affect the catalytic box.

Somatic

Loss of heterozygosity in developing tumors.

Implicated in

Familial cylindromatosis and multiple trichoepithelioma

Note

Familial cylindromatosis, also called turban tumor syndrome is a rare inherited cancer which is characterized by the formation of benign tumors, called cylindroma, in hairy parts of the body, mostly the scalp. Cylindroma are considered as originating from a transformation event specifically affecting the folliculo-sebaceous-apocrine unit that produces hair and its associated glands. Early observations established that affected patients are heterozygous at birth for the locus causing the disease, whereas the cylindroma they develop exhibit a loss of heterozygosity (LOH) demonstrating the involvement of a gene coding for a tumor suppressor. More recently, it has been shown that another genetic disease sharing similarities with familial cylindromatosis, multiple trichoepithelioma (MT), is also caused by CYLD mutations (For reviews, see Massoumi and Paus, 2007; Courtois, 2008; Amaro et al., 2009).

Various cancers

Note

Loss of CYLD has been reported in solid tumors of the colon and liver (Hellerbrand et al., 2007), kidney (Ströbel et al., 2002), cervix (Hirai et al., 2004) and prostate (Kikuno et al., 2008). CYLD is also epigenetically silenced in some non-small-cell lung cancers (NSCLC) (Zhong et al., 2007).

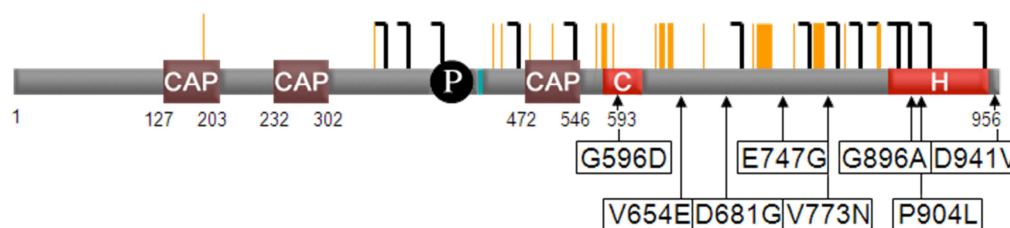


Figure 3. Mutations of CYLD. Misense mutations are indicated by boxes, nonsense mutations by black brackets and frameshift mutations by orange bars. Compiled from Blake and Toro, 2009 with additions from Amaro et al., 2009; Kazakov et al., 2009; Nasti et al., 2009; Wang et al., 2010 and Kazakov et al., 2010.

CYLD has been identified as inactivated by either mutation or deletion in multiple myeloma (Annunziata et al., 2007; Keats et al., 2007). In this specific case, CYLD inactivation has been associated with short-term survival (Jenner et al., 2007).

In the case of melanoma, it has been shown that the CYLD promoter region is under negative control by snail, a protein which is upregulated in this disease (Massoumi et al., 2009). CYLD down-regulation results in Bcl3/NF-kappaB activation.

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